From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/RU2004/000298	03.08.2004	04.08.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/502, A61K31/5025, A61P1/00, A61P5/02, A61P9/00, A61P9/12, A61P15/10, A61P25/16, A61P25/22,

Applicant
ZHILOV, Valery Khazmuratovich

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Langer, O Telephone No. +31 70 340-1972

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/RU2004/000298

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-15

because:

☒ the said international application, or the said claims Nos. 1-3, 10-13 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-3, 10, 11 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-3, 10, 11 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 4-9

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 2, 3, and partially 1, 10-13

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3, 10-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	12
	No:	Claims	1-3, 10, 11, 13
Industrial applicability (IA)	Yes:	Claims	-
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III.

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Article 34(4)(a)(i) PCT

Claims 1-3, and 11-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

III.2. Articles 5 and 6 PCT

III.2.1. Present claims 1-3, 10 and 11 relate to an extremely large number of possible pathological conditions, namely all pathological conditions (diseases) 'caused by disorders of a nitrergic system and /or dopaminergic system of an organism', and to a large number of pharmacological activities, including neuroprotective activity (claim 10), improvement of cognitive functions (claim 11) and normalization of the psychopysiological status (claim 11).

III.2.2. In fact, the claims contain so many variants that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

III.2.3. Consequently, the search for the International Search Report has been carried out for those parts of the application that relate to invention 1 and appear to be clear (and concise), namely those in relation to the treatment of the specific pathological conditions (diseases, disorders) explicitly defined in claims 12 and 13.

III.2.4. As the International Search Report for the present application has been limited to subject-matter as defined under item III.2.3, **this Written Opinion has been established only for those parts of the subject-matter of the present claims for which an International Search has been performed, namely those parts that have been specified under item III.2.3 above.**

Re Item IV.

Unity of Invention (Rule 13 PCT)

IV.1. The separate inventions/groups of inventions have been identified as follows:

IV.1.1. Claims 2, 3, and partially 1, 10-13
Use of compounds according to the general structural formula of claim 1, wherein A, Z = -CH= and B = -N=, i.e. the pyrido[2,3-d]-6H-pyridazine-5,8-diones of claims 2 and 3, in the treatment of diseases caused by disorders of a nitrergic system and/or dopaminergic system of an organism.

IV.1.2. Claims 4, 5, and partially 1, 10-13
Use of compounds according to the general structural formula of claim 1, wherein A, B, Z = -CH=, i.e. the benzo[d]-3H-pyridazine-1,4-diones of claims 4 and 5, in the treatment of diseases caused by disorders of a nitrergic system and/or dopaminergic system of an organism.

IV.1.3. Claims 6, 7, and partially 1, 10-13
Use of compounds according to the general structural formula of claim 1, wherein Z = -CH= and A, B = -N=, i.e. the pyrazino[2,3-d]-6H-pyridazine-5,8-diones of claims 6 and 7, in the treatment of diseases caused by disorders of a nitrergic system and/or dopaminergic system of an organism.

IV.1.4. Claims 8, 9, and partially 1, 10-13
Use of compounds according to the general structural formula of claim 1, wherein A = -CH= and B, Z = -N=, i.e. the pyrimido[4,5-d]-6H-pyridazine-5,8-diones of claims 8 and 9, in the treatment of diseases caused by disorders of a nitrergic system and/or dopaminergic system of an organism.

IV.2. The above inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

IV.2.1. The problem to be solved by the present application resides in the provision of pharmaceutical compositions for the treatment of diseases caused by disorders of a nitrergic system and/or dopaminergic system of an organism.

IV.2.2. The solution disclosed in the present application is to use a cyclic bioisostere of a purine system derivative according to the general structural formula of claim 1.

IV.2.3. Technical relationship between the different embodiments
The technical relationship between the different embodiments resides in the activity of the compounds according to the general structural formula of claim 1 towards nitrergic and dopaminergic systems.
Furthermore, the different chemical compounds for which a use is claimed are linked to each other by a common structural formula, namely the formula of claim 1.

IV.2.4. State of the art

The document EP-A-1203587

relates to a medicinal preparation comprising the sodium salt of 5-amino-2,3-dihydrophthalazine-1,4-dione having immunomodulatory, anti-inflammatory, and antioxidant properties (abstract).

The document RU-C-2169139

also discloses the use of alkali or alkali-earth salts of 5-amino-2,3-dihydrophthalazine-1,4-dione as anti-inflammatory and immunocorrecting agents (abstract).

The modulation of the immune system and the treatment of inflammations is one object of the present invention, see claim 13. The use of the compound 5-amino-2,3-dihydrophthalazine-1,4-dione is explicitly claimed in the present application (compound 15 of claim 4).

The document EP-A-0617024

discloses the use of 5-aminophthaloylhydrazide or of its sodium salt as - inter alia - anti-inflammatory agents (abstract).

The document EP-A-0617733

discloses the use of 5-aminophthaloylhydrazide or salts thereof for the treatment of psoriasis (abstract; claims 1 and 3).

The document WO-A-02/09681

discloses the use of amino-derivatives of 2,3-dihydrophthalazine-1,4-dione and of salts thereof as immunocorrecting agents, including the use for the treatment of acute gastroenteritis (abstract; page 1, last paragraph to page 3, paragraph 3; page 18, Table 10 (entry 'acute gastroenteritis').

The treatment of gastro-intestinal disorders, which encompasses the treatment of gastroenteritis, is explicitly claimed in the present application, cf. claim 13.

In the WPI abstract of the patent JP50046697,

the hypotensive and diuretic activities of the pyrido-pyridazine 7-phenyl-1,2,3,4-tetrahydropyrido[3,4d]pyridazine-1,4-dione is disclosed (WPI abstract)

IV.2.5. Special technical feature (Rule 13.2 PCT)

In view of the above disclosures, it appears that the use of compounds of the general structural formula of claim 1 for the treatment of diseases caused by disorders of a nitrergic system and/or dopaminergic system of an organism, including the treatment of the specific disorders mentioned in claim 12 and 13, is known in the prior art.

It is further known from JP50046697 that not only the homocyclic variants of the general structural formula of claim 1, i.e. the benzo[d]-3H-pyridazine-1,4-diones, but also the N-heterocyclic variants, in particular the pyrido[3,4-d]pyridazine-1,4-diones, have an activity as claimed in the present application.

For the above reasons, neither the general structural formula of claim 1, nor its N-heterocyclic subset (pyrido, pyrazino, pyrimido) can serve as 'special technical features' in the sense of Rule 13.2 PCT.

IV.2.6. Other technical features

No further technical features can be identified in the present application that could serve as 'special technical features' in the sense of Rule 13.2 PCT, thereby unifying the different inventions by a 'single general inventive concept' in the sense of Rule 13.1 PCT.

IV.2.7. The present application consequently lacks unity of invention. The different solutions not unified by a "single general inventive concept" in the sense of Rule 13.1 PCT are identified above.

Each of the different inventions is a separate invention, characterised by its particular technical effect, representing its contribution to the state of the art.

IV.2.8. Scope of this Written Opinion

An International Search Report has been established for invention 1, only. Therefore, this Written Opinion relates to the subject-matter in relation to invention 1.

Re Item V.

Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability

V.1. The following statement under Rule 43bis.1(a)(i) with regard to novelty and inventive step relates only to subject-matter as defined above under item III.2.3 and as far as relating to invention 1, defined above under item IV.1.1.

V.2. The following documents are referred to:

D1: EP-A-1 203 587 (PAVLOV ANATOLIY IVANOVICH ; ABIDOV MUSEA TAZHUDINOVICH (RU)) 8 May 2002 (2002-05-08)

D2: RU-C-2 169 139 (TS SOVREMENNOJ MEDITSINY MEDIK) 20 June 2001 (2001-06-20)

D3: EP-A-0 617 024 (LIMAD MARKETING EXP & IMP) 28 September 1994 (1994-09-28)

D4: EP-A-0 612 733 (LIMAD MARKETING EXP & IMP) 31 August 1994 (1994-08-31)

D5: WO 02/09681 A (MEDINKOR ZMM AG ; ZHILOV VALERII KHAZHMURATOVICH (CH)) 7 February 2002 (2002-02-07)

D6: DATABASE WPI Section Ch, Week 197533 Derwent Publications Ltd., London, GB; Class B02, AN 1975-54838W XP002312642 & JP 50 046697 A (TAKEDA CHEM IND LTD) 25 April 1975 (1975-04-25)

V.3. Novelty (Article 33(2) PCT)

The present application meets the requirements of Article 33(1) PCT with respect to novelty of the claims, because the subject-matter of claims 1-3 and 10-13, as far as relating to invention 1 (see item IV.1.1) and as far as restricted as indicated under item III.2.3, is new in the sense of Article 33(2) PCT.

V.3.1. Prior art
See item IV.2.4 for the disclosures of documents D1 to D6.

None of the documents D1 to D5 discloses the use of the pyrido[2,3-d]-6H-pyridazine-5,8-diones of claim 2 for a treatment according to item III.2.3.

V.3.2. For the above reasons, the subject-matter of present claims 1-3 and 10-13, as far as relating to invention 1 and as far as restricted as indicated under item III.2.4, is considered as new in the sense of Article 33(2) PCT over the prior art.

V.4. Inventive step (Article 33(3) PCT)

The present application does not meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1-3, 10, 11 and 13, as far as relating to invention 1, does not involve an inventive step in the sense of Article 33(3) PCT.

V.4.1. Problem to be solved
The problem to be solved by the present application resides in the provision of pharmaceutical compositions for the treatment of diseases caused by disorders of a nitrergic system and/or dopaminergic system of an organism, in particular for the treatment of diseases as defined in present claims 12 and 13.

V.4.2. Solution
The solution disclosed in invention 1 (as defined under item IV.1.1) of the present application is to use a cyclic bioisostere of a purine system derivative according to the general structural formula of claim 2.

V.4.3. Prior art

See item IV.2.4 for the disclosures of documents D1 to D6.

V.4.4. Difference between the application and the closest prior art

The difference between invention 1 of the present application and document D1, which has been selected as the closest prior art, resides in the use of Li, Na or K salts of derivatives of **pyrido**[2,3d]-6H-pyridazine-5,8-dione, instead of the sodium salt of 5-amino-2,3-dihydrophthalazine-1,4-dione (= **benzo**[d]-3H-pyridazine-1,4-dione, i.e. the **carba-analogue** of the compounds of the present application) as immunomodulating and anti-inflammatory agents.

V.4.5. Analysis of the presence of an inventive step

The person skilled in the art, knowing about the applicability of the compounds of document D1 as immunomodulating and anti-inflammatory agents, would, without the exercise of any inventive skill or ability beyond that to be expected from him, consider trying to use an aza-analogue of the known compounds for the above treatment. This structural modification of the synthetic target can be performed in a straightforward way by starting the synthesis from quinolinic acid instead of phthalic acid. Structural modifications of active compounds by single variations of this kind are obvious to the person skilled in the art and straightforward to perform.

This obvious modification of a pharmaceutic target cannot account for the presence of an inventive step for the subject-matter of claims 1-3, 10, 11 and 13, though.

V.4.6. Consequently, the presence of an inventive step in the sense of Article 33(3) PCT must be denied for the subject-matter of present claims 1-3, 10, 11 and 13.

V.4.7. The subject-matter of present claim 12 relates to the use of the compounds of the invention as anxiolytic and antidepressive agents. In the absence of relevant prior art, the subject-matter of present claim 12, as far as relating to the first invention, is considered as comprising an inventive step in the sense of Article 33(3) PCT.

V.5. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 1-3 and 11-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.